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Development of pandemic influenza vaccine production capacity in Viet Nam

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ABSTRACT

The Institute of Vaccines and Medical Biologicals (IVAC), a state-owned vaccine manufacturer, initiated research into avian influenza vaccines in the early 1990s in response to the threat of a highly pathogenic avian influenza pandemic. Successful results from laboratory studies on A(H5N1) influenza virus attracted seed funds and led to participation in the WHO technology transfer project to enhance influenza vaccine production in developing countries. IVAC's goal is to produce 500,000 doses of inactivated monovalent whole-virion influenza vaccine per year by 2012, and progressively increase capacity to more than 1 million doses to protect essential populations in Viet Nam in the event of an influenza pandemic. The WHO seed grants, supplemented by other international partner support, enabled IVAC to build in a very short time an influenza vaccine manufacturing plant under Good Manufacturing Practice and relevant biosafety standards, a waste treatment system and a dedicated chicken farm for high-quality eggs. Much of the equipment and instrumentation required for vaccine production has been installed and tested for functional operation. Staff have been trained on site and at specialized courses which provided comprehensive manuals on egg-based manufacturing processes and biosafety. Following process validation, clinical trials will start in 2011 and the first domestic influenza vaccine doses are expected in 2012.

1. Introduction

Viet Nam has been committed to influenza pandemic preparedness ever since a highly pathogenic avian influenza virus hit animal and human populations in Asia in 1990s. At that time, scientists from the Institute of Biotechnology pioneered the production of poultry vaccines against H5N1, which enabled the country to reduce dramatically avian and human disease incidence. In 2005, the Government of Viet Nam developed a national plan for human influenza vaccine production, within which the state-owned Institute of Vaccines and Medical Biologicals (IVAC) undertook preliminary research on egg-derived inactivated influenza vaccine A(H5N1) with positive laboratory results. These results, and strong domestic backing, encouraged IVAC to seek support to extend this research. Seed funding was found and IVAC was selected in 2007 as a grantee of the World Health Organization (WHO) pandemic influenza vaccine technology transfer initiative.

The goal of IVAC is to manufacturer 500,000 doses of monovalent influenza vaccine under appropriate biosafety and current Good Manufacturing Practice (cGMP) conditions, with the potential for expansion to >1 million doses per year. The specific objectives are to build and equip a small-scale manufacturing facility to produce egg-derived inactivated whole virion, alum adjuvanted influenza vaccine for pandemic use, complemented by a waste treatment system and a chicken farm to secure supplies of qualified clean eggs. Progress towards these objectives in 2008–2010 is described below.

2. Influenza manufacturing plant

Following evaluation of the dossier by WHO in May 2008 and a national tender process, a contractor was selected to design and construct a dedicated influenza vaccine production plant with a waste treatment system near IVAC in Nha Trang. In record speed, this facility was completed, certified cGMP-compliant and since June 2010 has been undergoing test operations within a validation programme. Much of the critical facility and process equipment has been procured and controlled for installation, operation, performance and maintenance qualification. The Master Validation Plan for influenza vaccine production was approved which contains the strategy for the validation of processes based on risk assessment, focusing primarily on sterility and viral safety.

To increase production capacity to at least 1 million doses per year, IVAC installed hot and cold rooms in a dedicated space, more incubator equipment and separate zones for in-process testing and the preparation of media and cleaning of equipment; inoculation and harvesting; and purification. Independent technical units have been set up to serve as a contaminated area, a noncontaminated area, and egg-handling and entrance, respectively. Each area is

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Table 1
Projected timeline to manufacture pandemic influenza vaccine.

Activity	Expected completion
Remaining critical equipment for validation procured	December 2010
Maintenance instruments and standards functional	December 2010
Quality eggs available from IVAC chicken farm	February 2011
Manufacturing standard operating procedures and master batch records validated	February 2011
Environmental programme for air and water fully operational	February 2011
Cleaning programme validated	February 2011
All training documented	March 2011
Performance qualification documents for all systems completed and approved with successful pre-licensure audit report	April 2011
Production of 3 consecutive lots for clinical trials initiated	June 2011
Good Laboratory Practice nonclinical toxicology studies completed	December 2011
Phase I clinical trials completed	March 2012
Phase II clinical trials completed	July 2012
Licensing process initiated for H1N1 and H5N1	December 2012

installed with separate heating, ventilation and air-conditioning (HVAC) systems. The HVAC systems and clean rooms have been qualified using a series of manufacturing runs, constant control of environmental conditions and digital direct controller system to stabilize room temperature, pressure and humidity. The quality control laboratory has been upgraded to meet international standards for influenza vaccine production and ancillary zones have been created for personnel.

The waste treatment system has been installed with high efficiency particulate air filters in outgoing airflows. Contaminated fluids from the production process are steam-sterilized before sending to the central fluid waste treatment station, and contaminated egg waste is kept in special bins for incineration after decontamination. A two-door autoclave for decontamination is in place, and a kill tank pressure vessel has been ordered, where liquids for decontamination will be collected and heated to 60–80 °C before disposal.

Standard operating procedures have been prepared for the operation and maintenance of each piece of equipment. IVAC is implementing an environmental control programme for air quality which meets particulate and microbiological specifications. Systems to ensure purified water and water for injection will become fully operational in 2011 (see Table 1).

3. Process validation batches

Onset of the A(H1N1) influenza pandemic in 2009 switched the focus from (A)H5N1 to the novel pandemic strain. Eight initial batches of H1N1 influenza whole virion vaccine were produced at a scale of 7000 eggs and used to test and improve the performance of the production process equipment and enhance the skills of IVAC staff. The first batch was produced with assistance from the Netherlands Vaccine Institute (NVI) and all process steps were evaluated. Valuable recommendations from international partners were immediately implemented to ensure that the next batches were improved. Optimal growth conditions were established and calibration procedures provided evidence for an inoculation dose of 0.16–0.24 ml per egg. Operators also became skilled in decapping and harvesting, clarification and filtration, zonal centrifugation and calibration to meet containment, biosafety and GMP standards. Optimal conditions for manual decapping are ongoing and have led to a reduction in the number of broken eggs. To optimize the harvester settings, the measurement for a harvested volume from 4 trays of 36 eggs was performed (Table 2). The Beta proprio lacton (BPL) method is now used for the inactivation process following a training course for IVAC staff at NVI in June 2010 and receipt of validation procedures. Corrective action also led to significant improvement in the evaluation of optical density and bioburden. The experience of this series of manufacturing runs of increasing size and complexity will allow IVAC to be able to perform successfully full-scale manufacturing lots. The performance qualification of all items, test runs and optimization of processes are expected to be completed by the end of 2010. After process validation runs, IVAC will produce three consecutive lots for preclinical trial and testing at IVAC, the National Institute for Control of Vaccine and Biologicals and international laboratories.

4. Chicken farm

In order to secure eggs of consistent high quality and yield from a controlled flock, a chicken farm was built, equipped and validated for full biosafety procedures. The farm comprises a 300 m^2 storage house with cages for chickens up to 4 months old, and a 1000 m^2 laying house for a maximum capacity of 7000 chickens over 4 months old. A pest and insect control system and a small laboratory to control the flock are also in place. Breeding was initiated in August 2010 following receipt of 3500 one-day-old chickens from France. Pending the availability of eggs from the IVAC farm in early 2011, eggs are being sourced from the Ministry of Agriculture under a protocol agreement to guarantee ample quantities under proper procedures. Chicken feed is supplied by a recognized company in Viet Nam to assure the quality and yield of eggs. Once fully operational, IVAC will be the sole qualified clean egg producer in Viet Nam, and will serve as a source for other national and potentially United Nations institutions.

The Ministry of Agriculture inspected the set up at regular intervals and following a successful audit, the facility, equipment and procedures of the chicken farm have been validated and documented within a maintenance programme, including standard operating procedures and training for personnel.

5. Skills development

IVAC has a history of compliance to GMP and ISO 9001 quality standards for its marketed products. For the influenza vaccine project, IVAC has benefited from the WHO collaboration to enhance the skills of its production and quality assurance and control staff. To date, four quality control staff from IVAC have been trained at the National Institute for Biological Standards and Control (NIBSC) during 1–2 week courses, and two quality assurance and six production

Table 2
Harvesting performance based on a volume from 4 trays with 36 eggs: optimal correlation between nozzle depth and harvest yield.

Test	Nozzle depth (mm)	Vacuum (times)	Bottle full (g)	Bottle empty (g)	Harvest (g)	Harvest (g/egg)
3	42	4	3225.0	1563.0	1662.0	11.54
1	44	4	3301.8	1512.5	1789.3	12.43
2	44	6	3744.6	1543.5	2201.1	15.29
4	46	4	3685.8	1554.1	2131.7	14.80
5	48	4	3778.9	1559.8	2219.1	15.41

staff were trained at NVI. These courses provided advice and hands-on experience in quality processes and procedures, laboratory and production scale process development and validation, and GMP production. In addition, a three-year consultancy agreement has been signed with NVI to cover the production process of egg-based influenza vaccine in IVAC's new facility, including on-site process validation, quality control and assurance, efficacy monitoring and (pre)clinical trials.

IVAC staff have also been trained in the installation, operation and maintenance of equipment by the relevant suppliers, along with concepts of safety and biosecurity related to specific machinery and for the chicken farm. Key personnel responsible for managing the chicken farm have also been trained in chicken husbandry by the Ministry of Agriculture in Hanoi.

6. Discussion

Applying our extensive knowledge in the manufacture and quality control of vaccines to published data, we succeeded in developing an A(H5N1) candidate vaccine in our research laboratory and have made significant progress over the last two years towards our goal to produce a pandemic influenza vaccine for the Vietnamese market. We have built, equipped and expanded a manufacturing facility to be able to produce >1 million doses per year as well as an operational poultry farm without the support of technology partner, and with only US$3.5 million seed funding from WHO to supplement the US$ 300 000 we were able to invest from our own funds. We have also managed to meet our original time frame despite challenges posed, for example, by the delayed arrival of funds and import authorization for materials.

By January 2011, when eggs from our chicken farm become available, we will initiate clinical studies to develop H1N1 and H5N1 vaccines. Subject to satisfactory results, IVAC plans to apply for registration and licensing of a monovalent H1N1 vaccine by the end of 2012, followed shortly afterwards by a monovalent H5N1 vaccine. At least 200,000 doses of H1N1 and 500,000 doses of H5N1 influenza will be stockpiled in 10-dose vials for essential populations in Viet Nam (elderly, health-care workers, pregnant women and persons at higher risk).

IVAC has decades of experience of working with leading vaccine R&D entities from all continents. A welcome effect of the WHO project has been interest from further international partners to support our research and expand our skills. We were selected, for example, as part of a grant from the USA to support, in particular, environmental aspects of our pandemic influenza project, and the development of Phases I and II safety and immunogenicity studies in human clinical trials of our vaccine. To this end a gap analysis was carried out during an on-site mission from PATH on outstanding measures needed to meet GMP quality clinical trial materials and biosafety standards. All elements of the gap analysis have been implemented satisfactorily. We also signed a protocol agreement in January 2010 with the Scientific Research Institute of Influenza of the Russian Academy of Medical Science for the joint development of vaccines, including clinical trials and adjuvants, as a strategic defence against highly pathogenic avian influenza virus.

The Government has been very supportive of IVAC's work, exemplified by the announcement of our WHO grantee status by the Prime Minister in January 2008. In addition, the Government has supported the development of A(H5N1) and A(H1N1) vaccines which, subject to successful testing, will enter production in Viet Nam in 2011 for free distribution to populations at high risk. The establishment of a seasonal influenza programme targeting the same population groups is also under consideration, which would ensure the sustainability of influenza vaccine manufacture in Viet Nam.

The fundamental strengths of IVAC in quality control and technology management, backed by its international partners, will assure the successful development and licensing of a pandemic influenza vaccine for the population of Viet Nam.

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